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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/840,872	04/25/2001	Antonio J. Grillo-Lopez	P 0280609/2000-30-154A	4921

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EXAMINER
NICKOL, GARY B

ART UNIT	PAPER NUMBER
1642	7

DATE MAILED: 10/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/840,872	Applicant(s) GRILLO-LOPEZ, ANTONIO J.	
	Examiner Gary B. Nickol Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *2,6 and 8-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Election filed August 2, 2002 (Paper No. 6) in response to the Office Action of July July 2, 2002 is acknowledged and has been entered. Claims 1-50 are pending in the application and Claims 2, and 6, and 8-50 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1, 3-5, and 7 are currently under prosecution.

Applicant's election with traverse of Group I, claims 1, and 3-5 in Paper No. 6 is acknowledged. (It should be noted that it appears that applicants inadvertently omitted Claim 7 in reference to their election of Group I, as Group I was restricted to Claims 1, 3-5, and 7 in Paper No. 5. Thus, in the interests of customer service, Claims 1, 3-5, and 7 will be examined). The traversal is on the ground(s) that the invention is novel and that the claims should be examined in their full scope. This is not found persuasive. MPEP 802.01 provides that restriction is proper between inventions that are independent or distinct. Here, the inventions of the various groups are distinct for the reasons set forth in Paper No. 5. Further, the inventions are classified differently, necessitating different searches in the US Patent databases. Also, the literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claim Objections

Claim 3 is objected to for reciting "lymphoma, (PCNSL)" because it appears the comma following the word "lymphoma" should be placed after "(PCNSL)". Appropriate corrections are requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, and 7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating a central nervous system (CNS) lymphoma in a mammal that has been diagnosed with said lymphoma, does not reasonably provide enablement for the claims as broadly drawn. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method of treating a central nervous system (CNS) lymphoma comprising the step of administering a therapeutically effective amount of an anti-CD20 antibody or fragment thereof wherein said anti-CD20 antibody is a chimeric.

The specification teaches (page 21, lines 23-27) that "treatment" refers to both therapeutic treatment *and prophylactic or preventive measures*. Those in need of treatment include those already with the disease or disorder as well as those in which the disease or disorder is to be prevented. Hence, the mammal may have been diagnosed as having the disease or disorder or may be predisposed or susceptible to the disease.

One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to treating or preventing a central nervous system lymphoma, and the specification provides insufficient guidance and objective evidence with respect to successfully preventing a central nervous system lymphoma or treating those predisposed or susceptible to a central nervous system lymphoma.

Reasonable guidance with respect to preventing any cancer (not just lymphomas) relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for

anyone susceptible to the disease. While various antibody-based therapeutics have shown some promising efficacy in the therapy of cancer, (Weiner L.M., Seminars Oncology, Vol. 26, No. 4, Suppl 12, pages 41-50, 1999), a recent review of such therapies did not indicate nor suggest that such therapies would be successful in the prevention of cancer. Furthermore, Weiner teaches (page 43) that one of the obstacles to successful monoclonal antibody therapy is insufficient target specificity. Thus, for an antibody to be somewhat successful there must be a target. In the case of the instant invention, the target is the CD20 antigen on B-cells, and the specification fails to contemplate the safety considerations in administering preventive monoclonal antibodies that would target all B-cells expressing the CD20 antigen in populations which might be susceptible to a central nervous system lymphoma.

Since the specification lacks the essential guidance of how to select for or screen those populations which would predictably benefit from preventive administration, and since the specification is silent on the safety and efficacy of applying the preventive agent to a specific population, it would require undue experimentation to practice the method as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Maloney *et al.* (Blood, Vol. 90. No. 6, 1997, pages 2188-2195.)

The claims are drawn to a method of treating a central nervous system (CNS) lymphoma comprising the step of administering a therapeutically effective amount of an anti-CD20 antibody or fragment thereof (Claim 1); wherein said anti-CD20 antibody is a chimeric (Claim 7).

Maloney *et al.* teach a method of treating low-grade or follicular non-Hodgkin's lymphoma (abstract) comprising the step of administering a therapeutically effective amount of an anti-CD20 antibody which is a chimeric antibody (see abstract, and page 2188, 2nd column, last paragraph). It is noted that the specification defines a central nervous system lymphoma as "any B cell lymphoma of the central nervous system". This can include Hodgkin's Disease lymphomas, non-Hodgkin's lymphoma, leptomeningeal metastasis and primary CNS lymphoma" (page 10, line 25). Thus, since the specification defines a CNS lymphoma as including non-Hodgkin's lymphoma, the prior art treatment of low-grade or follicular non-Hodgkin's lymphoma anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5, and 7 rejected under 35 U.S.C. 103(a) as being unpatentable over Maloney *et al.* (Blood, Vol. 90. No. 6, 1997, pages 2188-2195.) as further evidenced by Yoneda *et al.* (US Patent No. 5,626,845, 1997)

The claims are drawn to a method of treating a central nervous system (CNS) lymphoma comprising the step of administering a therapeutically effective amount of an anti-CD20 antibody or fragment thereof (Claim 1); wherein the anti-CD20 antibody fragment is selected from the group consisting of Fab, Fab', and $F(ab')_2$ (Claim 5); wherein said anti-CD20 antibody is a chimeric (Claim 7).

Maloney *et al.* teach as set forth above.

Maloney *et al.* do not teach wherein the anti-CD20 antibody fragment is selected from the group consisting of Fab, Fab', and $F(ab')_2$

Yoneda *et al.* teach that antibody fragments such as Fab, Fab', and $F(ab')_2$ are art-known substitutes for antibodies.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modulate the anti-CD20 antibody of Maloney *et al.* to engineer related antibody fragments including Fab, Fab', and $F(ab')_2$ because the production of such truncated antibodies are examples of art known substitutes for antibodies as evidenced by Yoneda *et al.* (Column 4, line 6). Further, one would have been motivated to do engineer and to expect success in using these fragments because it is well known in the art that such antibody fragments are smaller in size providing the advantage of improved tumor penetration and more rapid systemic clearance.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.

Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1,3, 5, 7 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,776,456 (Anderson *et al.*) as evidenced by Murphy *et al.* (Clinical Oncology, 2nd edition, 1995, American Cancer Society, Inc., pages 392,408) and Kuppers *et al.* (Ann Oncol, 1998, Vol. 9 Suppl 5, abstract) in further view of Yoneda *et al.* (US Patent No. 5,626,845, 1997).

Claim 1 of US Patent No. 5,776,456 is drawn to a method of treating a B cell lymphoma comprising administering a therapeutically effective amount of immunologically active chimeric anti-CD20 antibody to a human, said antibody being derived from a transfectoma comprising anti-CD20 in TACE 9, ATCC deposit number 69119.

The above claim constitutes a genus of B-cell lymphomas and a species of anti-CD20 antibody (TACE 9, ATCC deposit number 69119). Since the currently pending claims constitute a genus of anti-CD20 antibodies, the patented species of anti-CD20 antibody (TACE 9, ATCC deposit number 69119) is an obvious variation included in the genus pending claim. Further, claims 1,3 of the present invention are drawn to a method of treating a central nervous system lymphoma wherein the specification teaches (page 10, line 24) that a CNS lymphoma is *any* B-cell lymphoma- including those lymphomas listed in Claim 3 (primary CNS lymphoma, leptomeningeal metastasis, or Hodgkin's disease with CNS involvement). Thus, the species of

B-cell lymphomas in the presently claimed application anticipates the broader genus of the patented claims drawn to a method of treating *all* B-cell lymphomas. As further evidenced by Murphy *et al.* , (1) most primary CNS lymphomas are B-cell lymphomas (page 392, 1st column, 1st paragraph), (2) the most common primary tumors responsible for leptomeningeal carcinomatosis include carcinomas of the breast and lung, *non-Hodgkin's lymphoma*, melanomas, and adult acute leukemias (page 408, 2nd column, 1st paragraph). Furthermore, it is well established in the art that Hodgkin's disease typically represents clonal populations of B-lineage cells as evidenced by Kuppers *et al.* (Ann Oncol, 1998, Vol. 9 Suppl 5, abstract). Thus, since the current claims are species of the broader genus of B-cell lymphomas, it would be obvious to one of ordinary skill in the art to include other B-cell lymphomas such as those B-cell lymphomas associated with the central nervous system. Moreover, one would have been motivated to include such species of B-cell lymphomas since the patented claims are fully enabled (i.e., one would expect success) for treating all B-cell lymphomas.

Furthermore, although the claimed invention does not claim antibody fragments such as Fab, Fab', and $F(ab')_2$, it would have been obvious to one of ordinary skill in the art to modulate the chimeric anti-CD20 antibody of US Patent No. 5,776,456 to engineer related antibody fragments including Fab, Fab', and $F(ab')_2$ because the production of such truncated antibodies are examples of art known substitutes for antibodies as evidenced by Yoneda *et al.* (Column 4, line 6). Further, one would have been motivated to do engineer and to expect success in using these fragments because it is well known in the art that such antibody fragments are smaller in size providing the advantage of improved tumor penetration and more rapid systemic clearance.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1,3,5,7 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 5,776,456 (Anderson *et al.*) as evidenced by Muphy *et al.* (Clinical Oncology, 2nd edition, 1995, American Cancer Society, Inc.) and Kuppers *et al.* (Ann Oncol, 1998, Vol. 9 Suppl 5, abstract) in further view of Yoneda *et al.* (US Patent No. 5,626,845, 1997).

The claims are drawn to a method of treating a central nervous system (CNS) lymphoma comprising the step of administering a therapeutically effective amount of an anti-CD20 antibody or fragment thereof (Claim 1); wherein the CNS lymphoma is selected from the group consisting of: primary CNS lymphoma, leptomeningeal metastasis, or Hodgkin's Disease with CNS involvement (Claim 3), wherein the anti-CD20 antibody fragment is selected from the group consisting of Fab, Fab', and $F(ab')_2$ (Claim 5); wherein said anti-CD20 antibody is a chimeric (Claim 7).

US Patent No. 5,776,456 teaches a method of treating a method of treating a B cell lymphoma comprising administering a therapeutically effective amount of immunologically active chimeric anti-CD20 antibody to a human, said antibody being derived from a transfectoma comprising anti-CD20 in TACE 9, ATCC deposit number 69119 (Column 55).

The patent does not specifically teach treating a central nervous system lymphoma wherein the CNS lymphoma is selected from the group consisting of: primary CNS lymphoma,

leptomeningeal metastasis, or Hodgkin's Disease with CNS involvement; wherein the anti-CD20 antibody fragment is selected from the group consisting of Fab, Fab', and $F(ab')_2$

The specification teaches (page 10, line 24) that a CNS lymphoma is *any* B-cell lymphoma- including those lymphomas listed in Claim 2 (primary CNS lymphoma, leptomeningeal metastasis, or Hodgkin's disease with CNS involvement).

Murphy *et al.* , teach that (1) most primary CNS lymphomas are B-cell lymphomas (page 392, 1st column, 1st paragraph), (2) the most common primary tumors responsible for leptomeningeal carcinomatosis include carcinomas of the breast and lung, *non-Hodgkin's lymphoma*, melanomas, and adult acute leukemias (page 408, 2nd column, 1st paragraph).

Kuppers *et al* teach that that Hodgkin's disease typically represents clonal populations of B-lineage cells.

Yoneda *et al.* teach that antibody fragments such as Fab, Fab', and $F(ab')_2$ are art-known substitutes for antibodies.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the invention was made to modulate the invention claimed in US Patent No. 5776456 so as to include B-cell lymphomas of the central nervous system because such lymphomas merely represent species of the broadly claimed genus of B-cell lymphomas. As further evidenced by Murphy *et al.* , (1) most primary CNS lymphomas are B-cell lymphomas (page 392, 1st column, 1st paragraph), (2) the most common primary tumors responsible for leptomeningeal carcinomatosis include carcinomas of the breast and lung, *non-Hodgkin's lymphoma*, melanomas, and adult acute leukemias (page 408, 2nd column, 1st paragraph). Furthermore, it is well established in the art that Hodgkin's disease typically represents clonal populations of B-

lineage cells as evidenced by Kuppers *et al.* (Ann Oncol, 1998, Vol. 9 Suppl 5, abstract). Thus, since the current claims are species of the broader genus of B-cell lymphomas, it would be obvious to one of ordinary skill in the art to include other B-cell lymphomas such as those B-cell lymphomas associated with the central nervous system. Moreover, one would have been motivated to include such species of B-cell lymphomas since the patented claims are fully enabled (i.e., one would expect success) for treating all B-cell lymphomas. Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modulate the chimeric anti-CD20 antibody of US Patent No. 5,776,456 to engineer related antibody fragments including Fab, Fab', and $F(ab')_2$ because the production of such truncated antibodies are examples of art known substitutes for antibodies as evidenced by Yoneda *et al.* (Column 4, line 6). Further, one would have been motivated to do engineer and to expect success in using these fragments because it is well known in the art that such antibody fragments are smaller in size providing the advantage of improved tumor penetration and more rapid systemic clearance.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
October 22, 2002